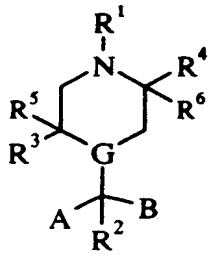
Claims

1. A compound of the general formula (I)



(I)

wherein

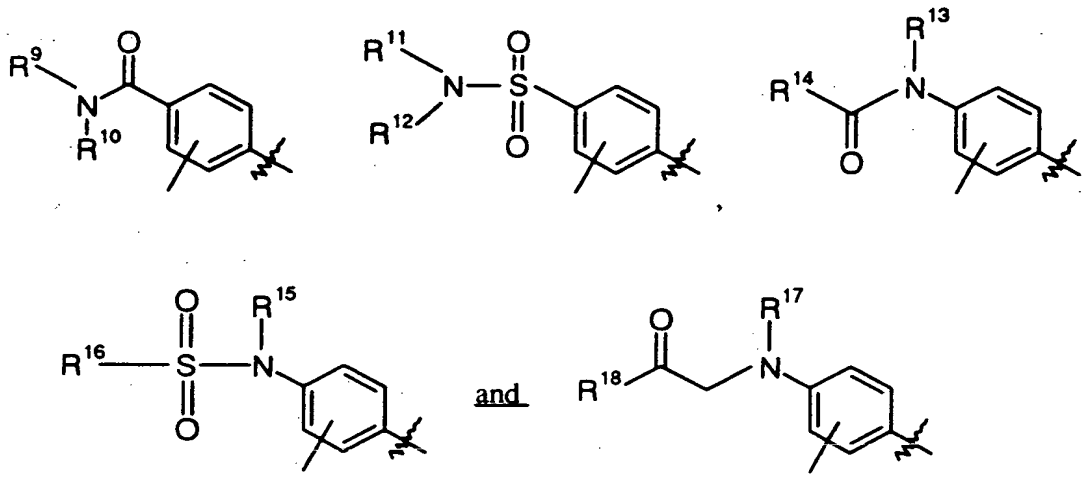
G is a carbon atom or a nitrogen atom;

A is selected from

(i) phenyl substituted by any of -COOH, - $CONH_2$, $COOCH_3$, -CN, NH_2 or $-COCH_3$;

(ii) naphtyl, benzofuranyl, and quinolinyl; and

(iii)



and

wherein the phenyl ring of each A substituent may be optionally and independently substituted by 1 or 2 substituents selected from hydrogen, CH_3, $(CH_2)_oCF_3$, halogen, $CONR^7R^8$, CO_2R^7, COR^7, $(CH_2)_oNR^7R^8$, $(CH_2)_oCH_3(CH_2)_oSOR^7$, $(CH_2)_oSO_2R^7$ and $(CH_2)_oSO_2NR^7R^8$ wherein o is 0, 1, or 2, and R^7 and R^8 are as defined below;

R^1 is selected from hydrogen; a branched or straight C_1-C_6 alkyl, C_1-C_6 alkenyl, -$CO(C_1$-C_6 alkyl); (C_1-C_6 alkyl)-B wherein B is as defined below; C_3-C_8 cycloalkyl, C_4-C_8 (alkyl-cycloalkyl) wherein alkyl is C_1-C_2 alkyl and cycloalkyl is C_3-C_6 cycloalkyl; C_6-C_{10} aryl; and heteroaryl having from 5 - 10 atoms selected from any of C, S, N and O; and whereby the C_6-C_{10} aryl and the heteroaryl may optionally be substituted by 1 or 2 substituents selected from hydrogen, CH_3, $(CH_2)_oCF_3$, halogen, $CONR^7R^8$, CO_2R^7, COR^7, $(CH_2)_oNR^7R^8$, $(CH_2)_oCH_3(CH_2)_oSOR^7$, $(CH_2)_oSO_2R^7$ and $(CH_2)_oSO_2NR^7R^8$; wherein o is 0, 1, or 2, and R^7 and R^8 are as defined below;

R^7 and R^8 is each and independently as defined for R^1 above;

R^2 is selected from hydrogen, CH_3, OR^1, CO_2R^1, and $CH_2CO_2R^1$ wherein R^1 is as defined above;

R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, R^{16}, R^{17}, and R^{18}, is each and independently as defined for R1 above;

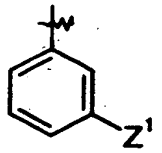
B is a substituted or unsubstituted aromatic; an optionally substituted C_5-C_{10} hydroaromatic; a heteroaromatic or a heterohydroaromatic moiety, each having from 5 to 10 atoms selected from any of C, S, N and O, and each being optionally substituted by 1 or 2 substituents independently selected from hydrogen, CH_3, CF_3, halogen, $(CH_2)_pCONR^7R^8$, $(CH_2)_pNR^7R^8$, $(CH_2)_pCOR^7$, $(CH_2)_pCO_2R^7$, OR^7, $(CH_2)_pSOR^7$, $(CH_2)_pSO_2R^7$, and $(CH_2)_pSO_2NR^7R^8$;

wherein p is 0, 1, 2 or 3 and wherein R^7 and R^8 are as defined above;

R^3, R^4, R^5 and R^6 is each and independently selected from R^7, $(CH_2)_pCONR^7R^8$, $(CH_2)_pNR^7R^8$, $(CH_2)_pCONR^7R^8$, $(CH_2)_pCO_2R^7$, $(CH_2)_pPh$, $(CH_2)_p$(p-OH Ph), $(CH_2)_p$-3-indolyl, $(CH_2)_pSR^7$, and $(CH_2)_pOR^7$;
wherein p is 0, 1, 2, 3, or 4, and R^7 and R^8 are as defined above;

as well as pharmaceutically acceptable salts of the compounds of the formula (I), isomers, hydrates, isoforms and prodrugs thereof;

with the proviso that when A is a phenyl ring substituted by a -CN group or by a $-NH_2$ group, B may not be



wherein

Z^1 is hydroxy, and esters thereof;

hydroxymethyl, and esters thereof; or

amino, and carboxamides and sulfonamides..

2. A compound of the formula I according to claim 1, wherein

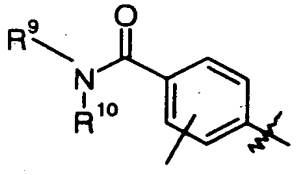
G is a carbon atom or a nitrogen atom;

A is selected from

(i) phenyl substituted by any of -COOH, - $CONH_2$, $COOCH_3$, -CN, NH_2 or -$COCH_3$;

(ii) naphtyl, benzofuranyl, and quinolinyl; and

(iii)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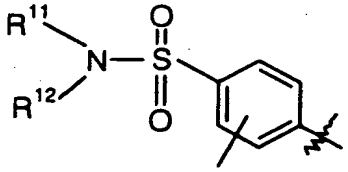
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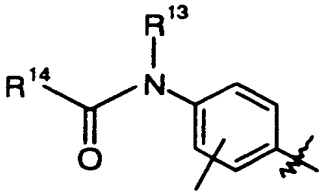

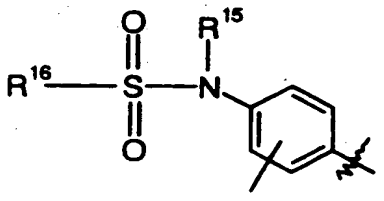
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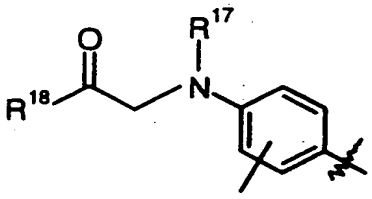

,

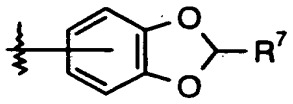
wherein the phenyl ring of each A substituent may be optionally and independently substituted by 1 or 2 substituents selected from hydrogen, CH_3, $(CH_2)_oCF_3$, halogen $CONR^7R^8$, CO_2R^7, COR^7, $(CH_2)_oNR^7R^8$, $(CH_2)_oCH_3(CH_2)_oSOR^7$, $(CH_2)_oSO_2R^7$ and $(CH_2)_oSO_2NR^7R^8$, wherein o is 0, 1, or 2, and R^7 and R^8 are as defined below;

R^1, R^7 and R^8 is each and independently selected from hydrogen; a branched or straight C_1-C_4 alkyl, allyl, -CO-(C_1-C_6 alkyl); (C_1-C_6 alkyl)-B wherein B is as defined below; C_3-C_5 cycloalkyl, C_4-C_8 (alkyl-cycloalkyl) wherein alkyl is C_1-C_2 alkyl and cycloalkyl is C_3-C_6 cycloalkyl; and phenyl;

R^2 is hydrogen, methyl, or OR^1 wherein R^1 is as defined above;

R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, R^{16}, R^{17}, and R^{18}, is each and independently as defined for R^1 above;

B is selected from phenyl, naphthyl, indolyl, benzofuranyl, dihydrobenzofuranyl; benzothiophenyl, pyrryl, furanyl, quinolinyl, isoquinolinyl, cyclohexyl, cyclohexenyl. cyclopentyl, cyclopentenyl, indanyl, indenyl, tetrahydronaphthyl, tetrahydroquinyl, tetrahydroisoquinolinyl, tetrahydrofuranyl, pyrrolidinyl, indazolinyl, and



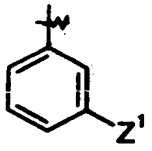
;

each B group being optionally substituted by 1-2 substituents independently selected from hydrogen, CH_3, CF_3, halogen, $(CH_2)_pCONR^7R^8$, $(CH_2)_pNR^7R^8$, $(CH_2)_pCOR^7$, $(CH_2)_p(CO_2R^7$, and OR^7,

wherein p is 0 or 1, and wherein R^7 and R^8 are as defined above; and

R^3, R^4, R^5 and R^6 is each and independently selected from hydrogen, CH_3, $CH(Me)_2$, $CH_2CH(Me)_2$, $CH(Me)CH_2CH_3$ $(CH_2)_pCONR^7R^8$, $(CH_2)_pNR^7R^8$, $(CH_2)_pCONR^7R^8$, $(CH_2)_pCO_2R^7$, $(CH_2)_pPh$, $(CH_2)_p$(p-OH Ph), $(CH_2)_p$-3-indolyl, $(CH_2)_pSR^7$, and $(CH_2)_pOR^7$, wherein p is 0, 1, 2, or 3, and wherein R^7 and R^8 are as defined above;

with the proviso that when A is a phenyl ring substituted by a -CN group or by a $-NH_2$ group, B may not be



wherein

Z^1 is hydroxy, and esters thereof;

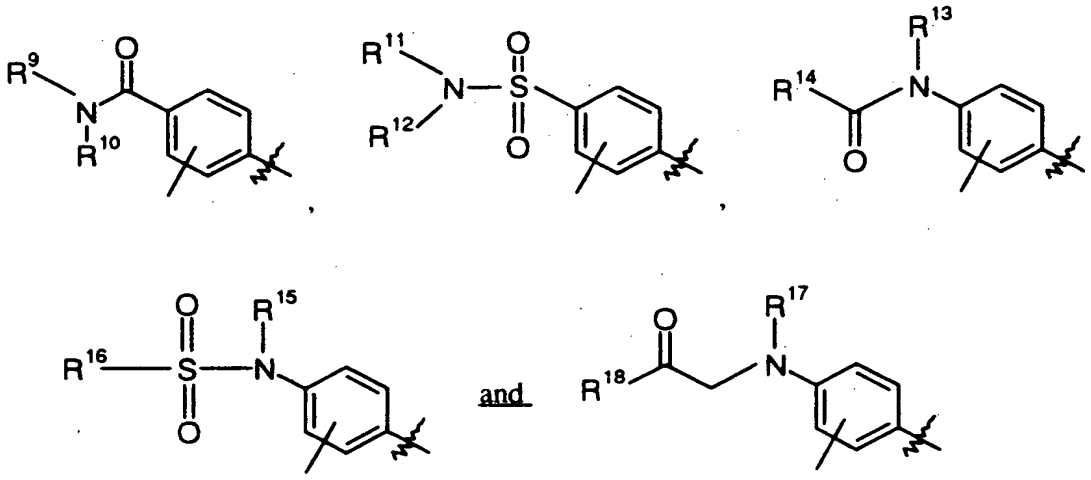
hydroxymethyl, and esters thereof; or

amino, and carboxamides and sulfonamides.

3. A compound of the formula I according to claim 1, wherein

G is a nitrogen atom;

A is selected from



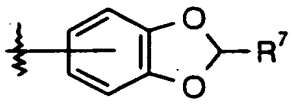
wherein

R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, R^{16}, R^{17}, and R^{18} is each an ethyl group;

R^1 is selected from hydrogen, methyl, ethyl, allyl, or CH_2-cyclopropyl;

R^2 is H, methyl, or OR^1;

B is selected from phenyl, naphthyl, indolyl, benzofuranyl, dihydrobenzofuranyl, benzothiophenyl, furanyl, quinolinyl, isoquinolinyl, cyclohexyl, cyclohexenyl, cyclopentyl, cyclopentenyl, indanyl, indenyl, tetrahydronaphthyl, tetrahydroquinyl, tetrahydroisoquinolinyl, tetrahydrofuranyl, indazolinyl, and



;

each B group being optionally substituted by 1-2 substituents independently selected from hydrogen, methyl, CF_3, halogen, $(CH_2)_pCONR^7R^8$, $(CH_2)_pNR^7R^8$, $(CH_2)_pCOR^7$, $(CH_2)_pCO_2R^7$, and OR^7,

wherein p is 0, 1, or 2, and wherein R^7 and R^8 are as defined for R^1 above;

R^3, R^4, R^5 and R^6 is each and independently selected from H, CH_3, $CH(Me)_2$, $CH_2CH(Me)_2$, $CH(Me)CH_2CH_3$ $(CH_2)_pCONR^7R^8$, $(CH_2)_pNR^7R^8$, $(CH_2)_pCONR^7R^8$, $(CH_2)_pCO_2R^7$, $(CH_2)_pPh$, $(CH_2)_p$(p-OH Ph), $(CH_2)_p$-3-indolyl, $(CH_2)_pSR^7$, and $(CH_2)_pOR^7$

wherein p is 0, 1 or 2, and wherein R^7 and R^8 are as defined above.

4. A compound of the formula (I) of claim 1 above, being anyone of

(±)-trans-1-(3-methoxy-α-(1-naphthyl)benzyl)-2,5-dimethylpiperazine (compound 3);
(±)-3-((αR*/S*)-α-((2S*,5R*)-4-Allyl-2,5-dimethyl-1-piperazinyl)-1-naphthyl)anisole (compound 4 and 5);
(±)-trans-1-(3-methoxy-α-(2-naphthyl)benzyl)-2,5-dimethylpiperazine (compound 8);
(±)-3-((αR*/S*)-α-((2S*,5R*)-4-Allyl-2,5-dimethyl-1-piperazinyl)-2-naphthyl)anisole (compound 9 and 10);
(±)-trans-1-(3-methoxy-α-(2'-benzofuranyl)benzyl)-2,5-dimethylpiperazine (compound 13);
(±)-3-((αR*/S*)-α-((2S*,5R*)-4-Allyl-2,5-dimethyl-1-piperazinyl)-2-benzofuranyl)anisole (compound 14 and 15);
(±)-3-((αR*/S*)-α-((2S*,5R*)-4-Cyclopropylmethyl-2,5-dimethyl-1-piperazinyl)-2-benzofuranyl)anisole (compound 16 and 17);
(±)-trans-1-(3-methoxy-α-(6'-quinolinyl)benzyl)-2,5-dimethylpiperazine (compound 20 and 21);
(±)-3-((αR*/S*)-α-((2S*,5R*)-4-Allyl-2,5-dimethyl-1-piperazinyl)-6-quinolinyl)anisole (compound 22);
(±)-3-((αR*/S*)-α-((2S*,5R*)-4-Allyl-2,5-dimethyl-1-piperazinyl)-6-quinolinyl)anisole (compound 23);
(±)-3-((αR*/S*)-α-((2S*,5R*)-4-Cyclopropylmethyl-2,5-dimethyl-1-piperazinyl)-6-quinolinyl)anisole (compound 24 and 25);
(±)-trans-1-(3-methoxy-α-(4-quinolinyl)benzyl)-2,5-dimethyl-piperazine (compound 28);
(±)-3-((αR*/S*)-α-((2S*,5R*)-4-Allyl-2,5-dimethyl-1-piperazinyl)-4-quinolinyl)anisole (compound 29 and 30);
(±) 4-((α-(1-Piperazinyl))-4-chlorobenzyl)-N,N-diethylbenzamide (compound 33);
(±) 4-((α-((4-Allyl)-1-piperazinyl))-4-chlorobenzyl)-N,N-diethylbenzamide • 2hcl (compound 34);
(±) 4-((α-(1-Piperazinyl))-2-naphtylmethyl)-N,N-diethylbenzamide (compound 37);
(±) 4-((α-((4-Allyl)-1-piperazinyl))-2-naphtylmethyl)-N,N-diethylbenzamide (compound 38);

(±) 4-((α-(1-Piperazinyl))-4-xylyl)-N,N-diethylbenzamide (compound 41);

(±) 4-((α-((4-Allyl)-1-piperazinyl))-4-xylyl)-N,N-diethylbenzamide • 2HCl (compound 42);

(±) 4-((α-(1-Piperazinyl))-3-xylyl)-N,N-diethylbenzamide • 2HCl (compound 45);

(±) 4-((α-(1-Piperazinyl))-cyclohexylmethyl)-N,N-diethylbenzamide (compound 48);

(±) 4-((α-(1-Piperazinyl))-3,4-dimethylbenzyl)-N,N-diethylbenzamide (compound 51);

(±) 4-((α-(1-Piperazinyl))-1-naphtylmethyl)-N,N-diethylbenzamide (compound 54);

4-(4-(2-Dimethyl-5-methyl-piperazinyl)-3-methoxybenzyl)-N,N-diethylbenzamide dihdrochloride (compound 57);

4-(4-(1-Allyl-2-dimethyl-5-methyl-piperazinyl)-3-methoxybenzyl)-N,N-diethylbenzamide dihydrochloride (compound 58);

4-(1-(4-Allyl-2-dimethyl-5-methyl-piperazinyl)-3-methoxybenzyl)- N,N-diethylbenzamide dihydrochloride (compound 60);

4-(1-(2-dimethyl-5-methyl-piperazinyl)-3-methoxybenzyl)-N,N-diethylbenzamide dihydrochloride (compound 61);

4-((1-piperazinyl)-benzyl)- N,N-diethylbenzamide dihydrochloride (compound 64);

4-((4-Allyl-1-piperazinyl)-benzyl)-N,N-diethylbenzamide dihydrochloride (compound 65);

4-((4-Acetyl-1-piperazinyl)-benzyl)- N,N-diethylbenzamide hydrochloride (compound 77);

4-(4-(2-Hydroxymethyl-5-methyl)piperazinyl-benzyl)-N,N-diethyl-benzamide dihydrochloride (compound 69);

4-((4-(2-Hydroxymethyl-5-methyl)piperazinyl)-3-methoxybenzyl)-N,N-diethylbenzamide dihydrochloride (compound 70);

4-((4-(1-Allyl-2-hydroxymethyl-5-methyl)piperazinyl)-3-methoxybenzyl)-N,N-diethylbenzamide dihydrochloride (compound 71);

Methyl 3-((2-naphtyl)-(3-methyl-piperazinyl)methyl)phenyl ether dihydrochloride (compound 75);

Methyl 3-((2-naphtyl)-(4-allyl-2-methyl-piperazinyl)methyl)phenyl ether dihydrochloride (compound 76);

4-((1-piperazinyl)-benzyl)-benzoic acid dihydrochloride (compound 79);

4-((1-piperazinyl)-benzyl)-N-ethylbenzamide hydrochloride (compound 83);

Methyl 4-((4-*t*-butoxycarbonyl-1-piperazinyl)-benzyl)benzoate (compound 80);

Methyl 4-((1-piperazinyl)-benzyl)benzoate dihydrochloride (compound 81);
4-(1-piperazinyl-benzyl)-benzonitril dihydrochloride (compound 84);
4-(1-piperazinyl-benzyl)-acetophenone dihydrochloride (compound 85);
4-((α-4-piperidinyl)-benzyl)-N,N-diethylbenzamide (compound 88);
N,N-Diethyl-4-(3-methoxybenzyl-1-piperazinyl)-benzamide (Example 50);
N,N-Diethyl-4-[(4-allyl-1-piperazinyl)-3-methoxybenzyl]-benzamide (Example 51);
4-[(N-benzyl-1-piperazinyl)-benzyl]-aniline (compound 91);
4-[(N-benzyl-1-piperazinyl)-benzyl]-acetanilide (compound 92);
4-[(N-benzyl-1-piperazinyl)-benzyl]-methanesulfonamide (Example 54);
Methyl-N-4-[(N-benzyl-1-piperazinyl)-benzyl]-2-methylacetate (Example 55); and
4-[(N-benzyl-1-piperazinyl)-3-fluorobenzyl]-acetanilide (compound 95).

5. A compound according to any of claims 1-4, in form of its hydrochloride salt.

6. A compound according to any of claims 1-5, for use in therapy.

7. A compound according to claim 6, wherein the therapy is pain management.

8. A compound according to claim 6, wherein the therapy is directed towards gastrointestinal disorders.

9. A compound according to claim 6, wherein the therapy is directed towards spinal injuries.

10. A compound according to claim 6, wherein the therapy is directed to disorders of the sympathetic nervous system.

11. Use of a compound according to any of claims 1-5 for the manufacture of a medicament for use in the treatment of pain.

12. Use of a compound according to any of claims 1-5 for the manufacture of a medicament for use in the treatment of gastrointestinal disorders.

13. Use of a compound according to any of claims 1-5 for the manufacture of a medicament for use in the treatment of spinal injuries.

14. A compound according to any of claims 1-5, further characterized in that it is isotopically labelled.

15. Use of a compound according to claim 14 as a diagnostic agent.

16. A pharmaceutical composition comprising a compound according to any of claims 1-5 as an active ingredient, together with a pharmaceutically acceptable carrier.

17. A process for the preparation of a compound according to any of claims 1-5, whereby

A) (i) An aldehyde or ketone is treated with a nucleophile, giving the corresponding alcohol;
(ii) the alcohol is converted into a suitable leaving group, which in turn is displaced with a nucleophile; and
(iii) a N-(4)-unsubstituted piperazine derivative is substituted via its organo halide or equivalent species, or acylated; or

B) (i) A N-protected amino acid ester is reacted with a second amino acid ester, and thereafter treated with an acid, giving a piparazinedione;
(ii) the dione is reduced to the corresponding piperazine; and
(iii) the piperazine is alkylated or acylated on one or more of the nitrogens.

18. A method for the treatment of pain, whereby an effective amount of a compound according to any of claims 1-5 is administered to a subject in need of pain management.